

Boundary Driven Open Markov System: A New Mathematical Framework for Nonequilibrium Biochemical Networks

Will Heuett
University of Washington
Department of Applied Mathematics

21 July 2005

Outline

- ★ Background and motivation for the new modeling framework

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Background and motivation for the new modeling framework

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Background and motivation for the new modeling framework

- ★ The goal is to model the reaction network of a living biochemical system.
- ★ Examples of modeling “open” reaction systems are:
 - ★ motor protein kinetic models
 - ★ and the Gillespie algorithm for simulations.
- ★ The grand canonical model has a niche.

The closed network model

Consider an irreducible system of monomolecular biochemical reactions involving N reactants. The dynamics of a single molecule can be modeled as a random walk,

$$\frac{dp_i(t)}{dt} = \sum_{\substack{j=1 \\ j \neq i}}^N (p_j(t)q_{j,i} - p_i(t)q_{i,j}).$$

Suppose there are a total of n molecules in the closed system. Then we have the joint probability

$$P(n_1, n_2, \dots, n_N, t) = \frac{n!}{n_1!n_2! \dots n_N!} (p_1(t))^{n_1} (p_2(t))^{n_2} \dots (p_N(t))^{n_N},$$

i.e. the multinomial distribution.

The closed network model (continued...)

If the system is closed to its surroundings, it will achieve equilibrium in which each reaction must be detailed balanced. Let π_i represent the probability of being in state i at equilibrium, then

$$\frac{\pi_i}{\pi_j} = \frac{q_{j,i}}{q_{i,j}} = K_{eq}$$

$$\frac{q_{i_0,i_1} q_{i_1,i_2} \cdots q_{i_m,i_0}}{q_{i_1,i_0} q_{i_2,i_1} \cdots q_{i_0,i_m}} = 1.$$

The detailed balance condition can be broken for “open” systems by fixing external concentrations that are typically absorbed into pseudo-first-order transition rate constants.

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The grand canonical model

Suppose there is an observer doing work on the system by keeping the number of molecules in state 0 equal to 1 and the number in state $N + 1$ equal to 0. The total number of molecules in this system will fluctuate. The expected number of molecules, $\langle n_i(t) \rangle$, at time t in state i satisfies

$$\frac{d \langle n_i(t) \rangle}{dt} = \sum_{\substack{j=0 \\ j \neq i}}^{N+1} (\langle n_j(t) \rangle q_{j,i} - \langle n_i(t) \rangle q_{i,j})$$

$\forall i \in \{1, 2, \dots, N\}$. The system is assumed to be empty initially, so the boundary and initial conditions are

$$\text{BCs: } \langle n_0(t) \rangle = 1, \quad \langle n_{N+1}(t) \rangle = 0$$

$$\text{ICs: } \langle n_i(0) \rangle = 0, \quad \forall i \in \{1, 2, \dots, N\}.$$

The grand canonical model (continued...)

The joint probability function for the open system is

$$P(n_1, n_2, \dots, n_N, t) = \prod_{i=1}^N \left[\frac{\langle n_i(t) \rangle^{n_i}}{n_i!} e^{-\langle n_i(t) \rangle} \right]$$

which means that the number of molecules in each state is independent and these random variables each have Poisson distributions.

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Variances and correlations

Let $\langle n_i \rangle^*$ be the number of molecules in state i when the system is in NESS and $\Delta n_i \triangleq n_i - \langle n_i \rangle^*$. It can be shown that the variances and covariances must satisfy

$$\begin{aligned} \frac{d \langle (\Delta n_i(t))^2 \rangle}{dt} &= \sum_{\substack{j=0 \\ j \neq i}}^{N+1} [(\langle n_j(t) \rangle + 2 \langle \Delta n_i(t) \Delta n_j(t) \rangle) q_{j,i} \\ &\quad + (\langle n_i(t) \rangle - 2 \langle (\Delta n_i(t))^2 \rangle) q_{i,j}] \\ \frac{d \langle \Delta n_i(t) \Delta n_j(t) \rangle}{dt} &= \sum_{\substack{k=0 \\ k \neq i}}^{N+1} (\langle \Delta n_j(t) \Delta n_k(t) \rangle q_{k,i} - \langle \Delta n_i(t) \Delta n_j(t) \rangle q_{i,k}) \\ &\quad + \sum_{\substack{k=0 \\ k \neq j}}^{N+1} (\langle \Delta n_i(t) \Delta n_k(t) \rangle q_{k,j} - \langle \Delta n_i(t) \Delta n_j(t) \rangle q_{j,k}) \\ &\quad - \langle n_i(t) \rangle q_{i,j} - \langle n_j(t) \rangle q_{j,i}. \end{aligned}$$

Variances and correlations (continued...)

The nonhomogeneous system of ODEs of the means can be rewritten as a homogeneous system of ordinary differential equations by substituting $n_i(t) = \Delta n_i(t) + \langle n_i \rangle^*$. In matrix form, the resulting system is written as

$$\frac{d \langle \Delta \mathbf{n}(t) \rangle}{dt} = \mathbf{Q} \langle \Delta \mathbf{n}(t) \rangle .$$

Using the solution of this system, the autocorrelation and cross-correlation functions of the number of molecules in each state can be shown to be

$$\begin{aligned} \langle \Delta n_i(t) \Delta n_i(0) \rangle &= e_{i,i}^{\mathbf{Q}t} \langle n_i \rangle^* = \sum_{k=1}^N \left(v_{i,k} e^{\lambda_k t} v_{k,i}^{-1} \langle n_i \rangle^* \right) \\ \langle \Delta n_j(t) \Delta n_i(0) \rangle &= e_{j,i}^{\mathbf{Q}t} \langle n_i \rangle^* = \sum_{k=1}^N \left(v_{j,k} e^{\lambda_k t} v_{k,i}^{-1} \langle n_i \rangle^* \right) . \end{aligned}$$

Variances and correlations (continued...)

The NESS flux of a reaction is related to the cross-correlation functions by

$$\begin{aligned}
 & \lim_{t \rightarrow 0} \frac{\langle \Delta n_j(t) \Delta n_i(0) \rangle - \langle \Delta n_i(t) \Delta n_j(0) \rangle}{t} \\
 &= \lim_{t \rightarrow 0} \frac{\sum_{k=1}^N \left(V_{j,k} e^{\lambda_k t} V_{k,i}^{-1} \langle n_i \rangle^* - V_{i,k} e^{\lambda_k t} V_{k,j}^{-1} \langle n_j \rangle^* \right)}{t} \\
 &= \sum_{k=1}^N \left(V_{j,k} \lambda_k V_{k,i}^{-1} \langle n_i \rangle^* - V_{i,k} \lambda_k V_{k,j}^{-1} \langle n_j \rangle^* \right) \\
 &= Q_{j,i} \langle n_i \rangle^* - Q_{i,j} \langle n_j \rangle^* \\
 &= q_{i,j} \langle n_i \rangle^* - q_{j,i} \langle n_j \rangle^* .
 \end{aligned}$$

Furthermore, the one-way NESS fluxes can be calculated from the initial slopes of the individual cross-correlation functions.

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Thermodynamics and reaction conductances

For the forward equation

$$\frac{d \langle n_i(t) \rangle}{dt} = \sum_{\substack{j=0 \\ j \neq i}}^{N+1} (\langle n_j(t) \rangle q_{j,i} - \langle n_i(t) \rangle q_{i,j}),$$

an associated backward equation exists. It can be written as

$$\frac{du_i(t)}{dt} = \sum_{\substack{j=0 \\ j \neq i}}^{N+1} [(u_j(t) - u_i(t)) q_{i,j}] \quad \forall i \in \{1, 2, \dots, N\}$$

$$\text{BCs: } u_0(t) = 1, \quad u_{N+1}(t) = 0$$

$$\text{ICs: } u_i(0) = 0, \quad \forall i \in \{1, 2, \dots, N\}$$

where

$$u_i(t) = \langle n_i(t) \rangle \frac{\pi_0}{\pi_i}.$$

Thermodynamics and reaction conductances (continued...)

The substitution allows for a physically meaningful potential function to be defined as

$$\mu_i(t) \triangleq \ln u_i(t) = \ln \langle n_i(t) \rangle - \ln \pi_i + \ln \pi_0.$$

and the chemical potential difference for a reaction between states i and j is

$$\Delta\mu_{i,j}(t) = \mu_i(t) - \mu_j(t) = \ln \frac{\langle n_i(t) \rangle q_{i,j}}{\langle n_j(t) \rangle q_{j,i}} = \ln \frac{J_{i,j}(t)}{J_{j,i}(t)}.$$

It follows that

$$(J_{i,j}(t) - J_{j,i}(t)) \Delta\mu_{i,j}(t) = (J_{i,j}(t) - J_{j,i}(t)) \ln \frac{J_{i,j}(t)}{J_{j,i}(t)} \geq 0,$$

which is equivalent to the second law of thermodynamics.

Thermodynamics and reaction conductances (continued...)

In terms of the chemical affinity, $u(t) = e^{\mu(t)}$, we have

$$\Delta u_{i,j}(t) = u_i(t) - u_j(t) = \frac{\langle n_i(t) \rangle \pi_0}{\pi_i} - \frac{\langle n_j(t) \rangle \pi_0}{\pi_j} = \frac{J_{i,j}(t) - J_{j,i}(t)}{\pi_i q_{i,j}} \pi_0$$

in which case

$$(J_{i,j}(t) - J_{j,i}(t)) \Delta u_{i,j}(t) = \frac{(J_{i,j}(t) - J_{j,i}(t))^2}{\pi_i q_{i,j}} \pi_0 \geq 0. \quad (1)$$

This result bears a likeness to the linear Ohm's Law of electrical circuit theory. Considering this, a reaction conductance can be defined as

$$c_{i,j} \triangleq \frac{J_{i,j}(t) - J_{j,i}(t)}{\Delta u_{i,j}(t)} = \frac{\pi_i q_{i,j}}{\pi_0} = c_{j,i}.$$

Thermodynamics and reaction conductances (continued...)

The system

$$\frac{du_i(t)}{dt} = \sum_{\substack{j=0 \\ j \neq i}}^{N+1} [(u_j(t) - u_i(t)) q_{i,j}] \quad \forall i \in \{1, 2, \dots, N\}$$

$$\text{BCs: } u_0(t) = 1, \quad u_{N+1}(t) = 0$$

$$\text{ICs: } u_i(0) = 0, \quad \forall i \in \{1, 2, \dots, N\}$$

is equivalent to a random walk, where $u_i(t)$ is the expected number of times a walk, starting at state i at time $t = 0$, reaches state 0 before reaching state $N + 1$ and does so before time t has passed.

Furthermore, when this system is in NESS, it is equivalent to an absorbing Markov chain, describing the expected number of times a random walk, starting at state i , reaches state 0 before reaching state $N + 1$.

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Conclusions and future work

- ★ The grand canonical models provide a full understanding of linear networks.
- ★ Possibly useful experimental methods can be suggested.
- ★ Currently we are studying the probability generating function and moment generating function approaches.
- ★ Further work needs to be done to generalize these methods to biochemical systems with bimolecular reactions.

Special Thanks

- ★ My advisor, Hong Qian
- ★ National Science Foundation VIGRE fellowship support
- ★ Department of Defense NDSEG fellowship support
- ★ SMB and ECMTB